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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,026	10/06/2000	Anthony Louis Devico	11076-002001	3193

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 12/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,026	DEVICO ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-9,11,13-16,24,35,37,38,40-46,49-57,60-63,65 and 73-79* is/are pending in the application.

4a) Of the above claim(s) *34,35,37,39-46,49-57,60-63 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 6-9, 11, 13-16, 24, 73-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed October 3, 2005 in response to the Office Action of June 3, 2005 is acknowledged and has been entered. Claims 1-3, 6-9, 11, 13-16, 24 and 73-79 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

Claims 1-3, 6-11, 13-16, 24 and 73-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the ability of the chimeric molecule to bind the co-receptor CCR5) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicants' arguments are focused on the specification. The argument is that the specification provides a written description for the claimed invention. Applicants cite to example IV of the specification as providing the requisite structure-function relationship to comply with the written description requirement. The argument is flawed in that the argument focuses on the structure function relationship set out in the specification when it is the claims that have to recite the structure function relationship. In order for the claims to comply with the

written description requirement the claims must recite the structure-function relationship. In this instance the INTERIM WRITTEN DESCRIPTION GUIDELINES specifically example 14 within the guidelines is directed to a claim that reads as follows: A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 (structure) **and catalyze the reaction of A→B (function)**.

Applicants' claims as written pertains to a structure that has variations but the structure is not limited to a particular function, thus the claims as are not presented as a structure-fucntion-claim. Although the specification has set out that the claimed chimeric structure binds to the co-receptor CCR5 (function) this limitation is not recited in the claims and the limitation is not read into the cliams. In this instance Applicants can overcome the rejection by reciting a specific function, wherein the chimera binds to the CCR5 co-receptor as measured by the to inhibit viral infection (see Response page 13, third paragraph). The claims of the instant invention are not presented as product-by-function claims. Limitation in the specification cannot be read into the claims.

The Court holding in *Capon V Eshhar* is that if the structure is known in the art (gp120 or CD4) then there is no need to recite them in the application. The Office did not require that Applicants recite specific sequences of the virus coat or CD4 (gp120 or CD4) in the specification. The Office indicated that the viral coat and the viral receptor as recited in the claims are indeterminate because the definition in the specification allows for an unlimited number of substitutions in the polypeptide sequences. The only functional language in the claim is that the composition has "the functionality of forming an intramolecular interacting complex," this language is insufficient to provide the structure function relationship as set out in example

14 of the written description guidelines. The claims are broadly drawn to a chimera between a virus coat and a virus receptor. The limitation of "the functionality of forming an intramolecular interacting complex" does not help define the structure/function relationship of the chimeric molecule because intramolecular forces are experienced by even very short amino acid sequences. Intermolecular interaction is a description of any process that involves a transfer (of atoms, groups, electrons, etc.) or interactions between two or more molecular entities (see IUPAC glossary terms I and M attached to the Office Action of April 5, 2004). Or intramolecular interaction is descriptive of any process that involves a transfer (of atoms, groups, electrons, etc.) or interactions between different parts of the same molecular entity. A molecular entity is any constitutionally or isotopically distinct atom, molecule, ion, ion pair, radical, radical ion, complex, conformer etc., identifiable as a separately distinguishable entity. In this instance the claims can read on a molecule comprising a truncated sequence of gp120 and CD4, the truncations can be extensive and can read on a chimera comprising single amino acids from bothe gp120 and CD4. There is not written description for the claims as they relate to a truncated molecule because the truncated molecule is not limited to a particular size for the truncation that is correlated with a function.

It remains the position of the Office that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The prior rejection is reiterate here: The instant invention is drawn to protein chimeras that comprise a virus coat polypeptide and a virus receptor polypeptide that are linked by an

amino acid sequence. The virus coat polypeptide and the virus receptor polypeptide are linked in such a way that allows for interaction between the coat and receptor components of the single chain molecule. The complex is further described as being capable of binding to a co-receptor. The specification provides the following definitions for the claimed coat polypeptide and receptor polypeptide:

> Page 9, lines 27 to page 10, line 4 defines "the term "receptor" to mean any polypeptide expressed by a cell that a virus can bind." This includes additional elements or molecules important for receptor conformation. Table 1 provides a list of contemplated virus/receptors complexes.

In the broadest interpretation the definition includes an antibody directed to a virus that is expressed on a cell surface of a recombinant cell.

> Page 15, line 1 to line 12 defines "the receptor and coat polypeptide sequences can be of any amino acid length. Preferably, they have a length that allows the polypeptide sequence to bind each other when in a chimeric polypeptide. Thus, receptor and coat polypeptide include native full-length receptor and full-length coat polypeptide sequences as well as parts of the polypeptide sequences. For example amino acid truncations, internal deletions or subunits of receptor, and coat polypeptide sequences are included."

> Page 15, lines 24-31. "in addition to the truncated, internally deleted and subunit polypeptide sequences, additional polypeptides sequence modifications are included. Such modifications include minor substitutions, variations, or derivitizations of the amino acid sequence of one or both of the polypeptide sequence that comprise the chimeric polypeptide, so long as the modified chimeric polypeptide has substantially the same activity or function as the unmodified chimeric polypeptide."

The definitions allows for unlimited deletions indicating that the ordinary artisan could not envision all the possible structures that may be encompassed by the instantly claimed invention. The limitation that the combination must be such that they have "substantially the same activity" does not provide a specific limitation because it does not define the interaction sufficiently that the ordinary artisan could envision the structures that are cable of accomplishing

this interaction before hand without more information. The definition also allows for an unlimited number of substitutions that encompass an indeterminate number of structures. Indicating that the structure must achieve a particular function does not help the ordinary artisan to envision the unlimited possibilities that would be encompassed by the instant claims.

The declaration under 37 CFR 1.132 filed by Dr. Anthony L. Devico in December 30, 2003 is insufficient to overcome the instant rejection because the declaration compares the Balgp120/sCD4 complex with the full length single chain chimeras (FLSC). The declaration is not commensurate with the full scope the claims. The claims can include chimeras that are less than full length and that include other viral proteins from SIV, FIV and FeLV. Applicant's declaration is directed to unexpected results achieved using the FLSC chimeras when compared to the complexes using a crosslinker set out in the patent. The data provided in the declaration does not show that all epitopes are occluded by the crosslinking procedure see the result using the 2G12 antibody. Applicant's showing of unexpected results is limited to the specific structures shown in the declaration and cannot be extrapolated to other single chain complexes or complexes using less than full-length structure. Claims limited to the FLSC chimera structure of HIV/CD4 would be allowable.

The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

> (MPEP 2163) The satisfaction of the enablement requirement does not satisfy the written description requirement. See *In re Barker*, 559 F.2d 588, 591, 194 USPQ 470, 472 (CCPA 1977) (a specification may be sufficient to enable one skilled in the art to make and use the invention, but still fail to comply with the written description requirement). See also *In re DiLeone*, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971). For the written description requirement, an applicant's specification must reasonably convey to

> those skilled in the art that the applicant was in possession of the claimed invention as of the date of invention. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997); *Hyatt v. Boone*, 146 F.3d 1348, 1354, 47 USPQ2d 1128, 1132 (Fed. Cir. 1998).
>
> The function of the description requirement is to ensure that the inventor had possession of, as of the filing date of the application relied on, the specific subject matter later claimed by him or her; how the specifica-tion accomplishes this is not material. *In re Herschler*, 591 F.2d 693, 700-01, 200 USPQ 711, 717 (CCPA 1979) and further reiterated in *In re Kaslow*, 707 F.2d 1366, 707 F.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983). See also MPEP § 2163 - § 2163.04.

In this instance applicants are claiming a chimera wherein neither the viral coat nor the viral receptor have not been sufficiently described in terms of their structure and function. Applicants are claiming a product, where the product is defined based on function (forming an intra molecular bond) without providing any information regarding the structure other than those specific structures disclosed in the specification and declaration. The viral coat and the viral receptor being recited is indeterminate because the definition in the specification allows for an unlimited number of substitutions in the polypeptide sequences. Claiming a product based on function (i.e. that the viral coat protein and receptor protein are capable of interacting) does not provide sufficient description of the product as claimed. It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. Therefore, structurally unrelated "molecules" encompassed by the claimed invention other than those disclosed in the specification as filed would be expected to have greater differences in their structural and functional characteristics and attributes. Mere idea or function is insufficient for written description.

"a mere wish or plan" for obtaining an invention is not enough to comply with § ll2, ¶ 1(*Regents of the University of California v. Eli Lilly & Co., 119* F.3d 559, at 1566).

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

The instant specification and claims do not provide sufficient functional and structural characteristics of the changes that are permissible in the viral coat protein and the viral receptor proteins and still maintain their function. Since the disclosure fails to describe the common attributes or characteristics that identify members of the group, the disclosure of particular compounds is insufficient to describe the genus of molecules, encompassed by the claimed invention.

In this instance applicants are claiming a chimera wherein neither the viral coat protein nor the viral receptor protein have been sufficiently described in terms of their structure and function to encompass all virus and coat protein chimeras of known viruses and yet undiscovered viruses. Therefore, there is lack of written description in the instant invention for the claimed chimeric structures.

Even a single amino acid change or mutation can destroy the function of a molecule in many instances, albeit not in all cases. The effects of these changes is largely unpredictable as to which ones have a significant effect versus not. Several publications document this unpredictability of the relationship between sequence and function, albeit that certain specific

sequences may be found to be conserved over polypeptides of related function upon a significant amount of further research. See the following publications that support this unpredictability as well as noting certain conserved sequences in limited specific cases [see Baker et al., Protein structure predication and structural gemonics. Science (2001) Vol. 294, No. 5540, pages 93- 96; Attwood, T. The babel of bioinformatics. Science (2000) Vol. 290, no. 5491, pages 471-473]. The specification provides no guidance as to which of nucleic acids and their corresponding amino acids may be changed while peptide activity is retained, the change of even a single amino acid can have a profound effect on the activity of a protein [Riffkin et al. A single amino-acid change between the antigenically different extracellular serine protease V2 and B2 from Dichelobacter nodous. Gene (1955) Vol. 167, pages 279-283]. The fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable [e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction,1994, Edited by Merz et al., (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495]. It is apparent that on the basis of Applicants' disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of polypeptide sequences as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of polypeptide sequences that must exhibit the disclosed biological functions as contemplated by the claims.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine reside at position 118 of acidic fibroblast growth factor

by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein [Burgess et al. Possible dissociation of the heparin-binding and mitogenic activities of heparin binding growth factor-1 from its receptor-binding activities by site directed mutagenesis of a single lysine residue. Journal of Cell Biology. (1990) Vol. 111, p 2129-2138]. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen [Lazar et al. Transforming growth factor alpha; mutations of aspartic acid 47 and leucine 48 results in different biological activities. Molecular and Cellular Biology (1988) Vol. 8, No. 3, p 1247-1252]. Similarly it has been shown that a glycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies [Tao et al. Studies of aglycosylated chimeric mouse-human IgG. The Journal of Immunology (1989) Vol. 143 No. 8, p. 2595-2601]. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Changes in the amino acid sequence of the antigen can have a direct effect on the ability of the antibody to bind the protein, furthermore, the changes that effect the antibody binding do not have to occur within the epitope binding region [Abaza et al. Effects of amino acid substitutions outside an antigenic site on protein binding to monoclonal antibodies of predetermined specificity obtained by peptide immunization. Journal of Protein Chemistry (1992) Vol. 11, No. 5, pages 433-444. Nuss et al. Defining the requirements for an antibody epitope on influenza virus neuraminidase: How Tolarant are protein epitopes? Journal of

Molecular Biology (1994) Vol. 235, pages 747-759]. A single point mutation in HIV alters the structure of the polypeptide to such an extent that neutralizing antibody will no longer recognize the sequence [di Marzo et al. Loss of a neutralizing epitope by a spontaneous point mutation in the V3 loop of HIV-1 isolated from an infected laboratory worker. Journal of Biological Chemistry (December 1993) Vol. 268, No. 34, pages 25894-25901].

The mere contemplation of the claimed genus in the specification is not sufficient to support the presently claimed invention directed to a genus of polypeptide including the viral coat and viral receptor chimera that may interact. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of polypeptide sequences that must possess the biological properties as contemplated by applicants' disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and . *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1405 (Fed. Cir. 1997). Possession may be shown by actual reduction to practice (as privded in the specification and the 37 U.S.C. 1.132 declaration), clear depcription of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics. Inc.*, 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a chimera sequences encoding a viral coat protein and a viral receptor protein including the unlimited

number of amino acids substitutions that are contemplated in the invention. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Conclusion

Claims 1-3, 6-11, 13-16, 24 and 73-79 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of

such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 12/23/05